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Prospective Memory in Healthy Aging, Subjective Cognitive Decline and Mild Cognitive Impairment

A Magnetic Resonance Imaging Study

Prospective Memory in Healthy Aging, Subjective Cognitive Decline and Mild Cognitive Impairment: A Magnetic Resonance Imaging Study

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Abstract

Prospective memory (PM) is defined as remembering when an action needs to take place following a cue (event-based or time-based). Alzheimer's Disease (AD) patients have an impairment in PM and almost 50% of patients with mild cognitive impairment (MCI) are expected to develop AD. Recent research has focused on a potential pre-MCI stage named Subjective Cognitive Decline (SCD) in which subjects perform similar to healthy individuals in standard tests yet declare a decline in their everyday memory functioning. We propose that PM might provide a more valuable insight into individual's everyday memory functioning, which is not necessarily reflected in standard tests. Furthermore, neuroimaging studies show that atrophy in specific brain regions (e.g. rostral prefrontal cortex) is linked with impairment in PM. This study aimed to investigate the role of PM tasks as an early marker of functional decline in preclinical AD populations and explore potential links with cortical thickness as a proxy of brain structure. 84 participants including healthy controls (HC) (n=26), people with SCD (n=29) and patients with MCI (n=29) were tested using cognitive assessments including three event-based PM tests from the Rivermead Behavioural Memory Test-3 and the Nottingham Extended Activities of Daily Living Scale (NEADL). Most participants also underwent structural MRI to examine cortical thickness. Findings showed PM performance to be correlated with NEADL scores, suggesting a decline in PM reflects a decline in independent functioning. Furthermore, PM was found to be correlated with average whole brain cortical thickness. In group-based analyses, patients with MCI performed significantly worse than HC and SCD groups in all aspects of PM. These findings suggest that PM tasks could provide good insight into everyday functioning in individuals at risk of developing dementia. Thus, PM tasks could be implemented into clinics to provide a useful guide to 'everyday' functional decline in incipient AD.

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First and foremost, I would like to thank my colleague Alfie Wearn (PhD Candidate) and my supervisors Dr Liz Coulthard and Prof Risto Kauppinen for their support and guidance throughout my MSc (by research) degree. Furthermore, I would like to thank the other MSc and undergraduate students: Candida Stainer, Ben Kershaw, Ellen Gaaikema, Lucy Adams and Emma Hadley who have contributed to the collection of data presented in this study. I would also like to thank the CRiCBristol staff who have been extremely helpful with day-to-day running of the study as well as providing expert help when required. Lastly, a huge thank you to all of our participants who dedicated their time to take part in dementia research.

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Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is my own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: ..... DATE: .....

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List of Abbreviations

AD	Alzheimer's Disease
NIA-AA	National Institute of Aging and the Alzheimer's Association
MCI	Mild Cognitive Impairment
PM	Prospective Memory
SCD	Subjective Cognitive Decline
HC	Healthy Control
rPFC	Rostral Prefrontal Cortex
TP	Temporal Pole
ROI	Region of Interest
ACE-III	Addenbrooke's Cognitive Examination – III
MRI	Magnetic Resonance Imaging
CDR	Clinical Dementia Rating
RBMT-3	Rivermead Behavioural Memory Test – 3
ADLQ	Activities of Daily Living Questionnaire
BCRS	Brief Cognitive Rating Scale
NEADL	Nottingham Extended Activities of Daily Living
DASS 21	Depression, Anxiety and Stress Scale 21
CVLT-2	California Verbal Learning Test – II
PAL	Paired Associates Learning
ROCFT	Rey-Osterrieth Complex Figure Test
OP	Occipital Pole
ANOVA	Analysis of Variance
IQ	Intelligence Quotient
SD	Standard Deviation

1. Introduction

1.1 Alzheimer's Disease – The Early Diagnosis Problem

Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterised by cognitive and functional impairment accompanied by changes in behaviour (McKhann et al., 1984). The increasing prevalence of AD is currently viewed as a global healthcare crisis with an enormous cost to the UK economy (Prince et al., 2014). The number of people living with AD is rapidly increasing, with more than 46 million AD patients globally and this number is forecast to double every two decades (Prince et al., 2015). In line with the diagnostic criteria published by McKhann *et al.* (1984), to provide a definitive AD diagnosis, a post-mortem brain examination was required to confirm the presence of amyloid plaque accumulation and neurofibrillary tangles of hyperphosphorylated tau. Tau protein plays a role in promoting the stability of microtubules, which is critical for normal neuronal functioning (Köpke et al., 1993). The abnormal hyperphosphorylation of tau leads to the formation of intraneuronal tangles, leading to neurofibrillary degeneration, which is one of the hallmark characteristics of AD (Arriagada et al., 1992). The new guidelines determined by the National Institute of Aging and the Alzheimer's Association (NIA-AA) has led to the revision and update of the clinical diagnostic criteria. In accordance with these changes, the evidence of biomarkers is used to inform diagnostic formulations (McKhann et al., 2011).

AD is seen as a disease spectrum where patients are thought to go through a long asymptomatic disease phase, undergoing vast neuropathological changes during this period, yet remaining cognitively "normal" (Dubois et al., 2010;Amieva et al., 2008;Bertens et al., 2015). This preclinical disease stage precedes the symptomatic (prodromal) stage of AD, which involves progressive decline in cognition, followed by functional impairment and eventually "full-blown" dementia (Villemagne et al., 2013;Wilson et al., 2011;Amieva et al., 2008). A study of community-dwelling individuals (N = 693) used an extensive neuropsychological test battery and revealed that early detection of cognitive changes in people at risk of developing dementia is possible (Saxton et al., 2004). The combination of diagnostic guidelines produced by the International Working Group and NIA-AA utilises the presence of

biomarkers to identify prodromal or preclinical stages of AD (Dubois et al., 2007;Jessen et al., 2014;Dubois et al., 2014;McKhann et al., 2011). Hence, it is possible to diagnose prodromal stages of AD, known as Mild Cognitive Impairment (MCI) (Albert et al., 2011;McKhann et al., 2011).

Despite a plethora of potential biomarkers, relatively few have made it into the clinical sphere due to expense, lack of validity and/or invasiveness. The mainstay of dementia diagnosis is still to use brief neuropsychological testing and structural imaging (usually Computerised Tomography scans) (Davis et al., 2013). There is a lack of tests with diagnostic accuracy that can predict patients with MCI who will progress onto developing AD dementia. Using ecologically valid tests of day-to-day function could allow us to identify and target an earlier disease stage reflecting the real impact of pathologies that will lead to dementia. One critical feature of biomarkers is that they identify the presence of pathology in the brain. Yet, it is known that brain pathology does not always lead to functional decline (Iacono et al., 2009). Therefore, biochemical and structural tests need to run alongside behavioural tests to identify the earliest deterioration in day-to-day function. By doing so, we can identify patients in need of early treatment and track its effects. Based on the evidence narrated above, one of the aims of this study is to investigate the relationship between an ecologically valid neuropsychological assessment tool and activities of daily living in people with preclinical AD or populations at-risk of developing AD. One potential method of identifying early changes in everyday functioning is thought to be through prospective memory performance, which will be described in the next section.

1.2 Prospective Memory – Definition, Relevance and Importance

Prospective Memory (PM) is defined as remembering when an action needs to be performed at the appropriate time. An example of PM would be remembering to buy a bottle of milk on the way back from work (event-based PM) or remembering to turn the hob off in 20 minutes time (time-based PM). In contrast to retrospective memory, which deals with remembering events that happened in the past, PM deals with actions to be undertaken in the future. Craik suggested PM depends more on

internal control mechanisms, relative to retrospective memory (Craik, 1983;Craik, 1986). These cognitive mechanisms involve recollection through the reconstruction of events in memory, which is directed by either external cues, such as a prompt from the experimenter, or self-initiated (internal) cues (Craik, 1986).

The complex process of PM has been categorised into four stages: (i) intention formation and encoding, (ii) retention of intention, (iii) intention initiation and (iv) execution of intended action (Kliegel et al., 2000). PM is suggested to be one of the most demanding cognitive processes due to being highly dependent on self-initiated retrieval, which is controlled by systems of the prefrontal cortex (Craik, 1986;Kliegel et al., 2000).

PM can be divided into two types; event-based PM and time-based PM (Einstein et al., 1992). The former is triggered by an external prompt (i.e. an event), whereas the latter requires the participant to undertake an action at a specific time (Einstein and McDaniel, 1990;Einstein et al., 1995). Amongst the two types of PM, time-based PM is suggested to be more dependent on mechanisms of internal control such as self-initiated time monitoring, with the assumption of no mnemonic or 'memory aids' being used (d'Ydewalle et al., 2001). Hence, due to the strong aspect of self-initiation, time-based PM is deemed more susceptible to age-related deterioration (Maylor, 1995;Einstein et al., 1995). Furthermore, PM is divided into two principal components, which are the prospective component and the retrospective component. The prospective component is the ability to recognise the appropriate cue in which the action is to be performed, also called "cue identification". The retrospective component is remembering what the action to be performed is, also called "intention retrieval" (McDaniel and Einstein, 1992).

PM forms a crucial part of independent daily functioning and causes significant decrement in independence when impaired (Kliegel and Martin, 2010;Burgess et al., 2000). Around 50-80% of all reported everyday memory problems consist of some form of PM impairment (Terry, 1988;Crovitz and Daniel, 1984). Furthermore, PM carries significant clinical relevance with multiple studies reporting high prevalence (around 40%) of patients visiting memory clinics with problems in PM (Fortin et al.,

2002;Kliegel and Martin, 2010). One interesting further question is determining theoretically the similarities or differences between PM and retrospective memory (Kliegel and Martin, 2010). We know that delayed memory (i.e. retrospective memory) is one of the most widely used and sensitive tests for early AD (Locascio et al., 1995;Pasquier, 1999;Albert, 1996). The extent to which PM would tell us more about developing AD than tests of delayed memory is highly clinically relevant but is, as yet, relatively underexplored.

Here, we sought to explore PM's influence on activities of daily living and how PM is impaired in people destined to develop AD. The next section will focus on the specific PM impairment in AD and preclinical AD populations.

1.3 PM in Alzheimer's Disease and Mild Cognitive Impairment

PM plays a fundamental role in independent living, and has a significant impact on quality of life when impaired (Burgess et al., 2000). Several studies reported evidence regarding the impairment of PM at very early stages of AD (Maylor et al., 2002;Huppert and Beardsall, 1993;Huppert et al., 2000). One of the striking findings was that PM tests were found to be more sensitive to early stages of dementia compared to conventional tests of retrospective (delayed) memory (Huppert and Beardsall, 1993). Hence, suggesting tests of PM have the potential to act as an indicator of early decline in cognition. Another study by Jones *et al.* (2006) provided further evidence regarding PM impairment in preclinical AD, where patients exhibited deficits in both prospective and retrospective components of PM. Additionally, authors reported an independent contribution of PM performance in predicting progression to AD, more so than that of retrospective memory (Jones et al., 2006). Yet, PM tests are not routinely used in clinics for diagnostic purposes. Most of the recent dementia research has focused on finding new biomarkers for early diagnosis (e.g. see review by (Barber, 2010)), however, we also need a guide to functional changes.

Recent research focused on extensively studying PM in preclinical or prodromal stages of AD (i.e. MCI). MCI lies within the cognitive spectrum that spans normal

healthy aging and AD dementia. Researchers defined MCI as a diagnostic entity in which an individual presents specific deficits in cognition (e.g. executive functions, declarative memory or visuospatial abilities) and performs below the norm in standard psychometric tests, yet their functional abilities remain intact (Petersen, 2004). Many studies demonstrated that PM is impaired in MCI, specifically in amnestic type (Kazui et al., 2005). Patients with amnestic MCI are the ones with a specific deficit in declarative memory, whereas patients with other cognitive deficits are categorised as non-amnestic MCI (Petersen, 2004).

PM impairment in patients with MCI is more prominent in time-based PM tasks, compared to event-based ones (Troyer and Murphy, 2007;Karantzoulis et al., 2009). Furthermore, Karantzoulis *et al. (*2009) suggested that PM deficiency in amnestic MCI could be due to impaired cue identification, which forms a crucial part of PM particularly in the “intention initiation” stage. The next step would be to explore whether such differences in cue-identification (i.e. prospective component of PM) is predictive of future cognitive decline. The results of such investigation could improve identifying the subset of patients within the MCI group that are destined to develop AD dementia. Hence, with early detection, we might be able to target the disease at a more critical stage where treatment opportunities are much higher (i.e. prior to significant brain atrophy).

MCI has become a recognised and clinically used diagnostic criterion, with approximately 10% chance of developing AD per year (Mitchell and Shiri-Feshki, 2009;Petersen, 2004). To be diagnosed with MCI, patients need to perform poorly on at least one cognitive test. However, we know that patients have symptoms even before they perform badly on standard tests. Hence, a great deal of attention is being paid to the new suggested category of a pre-MCI population called Subjective Cognitive Decline (SCD). SCD at the stage of normal cognition is associated with an increased risk of developing AD pathology and cognitive decline progressing to AD dementia (Glodzik-Sobanska et al., 2007;Reisberg et al., 2010;Wang et al., 2013;Petersen et al., 2001). Despite not yet being clinically used, SCD is defined for research purposes and has about 5-10% chance of progressing to MCI, which can lead to developing AD (Fernandez-Blazquez et al., 2016). Most of the evidence regarding the link between SCD and AD comes from neuroimaging studies showing

a decrease in the volume of the hippocampus, entorhinal cortex, frontotemporal pole and corpus callosum in the SCD group (Saykin et al., 2006;van Norden et al., 2008;Wang et al., 2006). Individuals with SCD do not differ from Healthy Controls (HC) in standard neuropsychological tests, however, they do differ in their PM performance, where SCD group performs worse than HCs in PM (Lee et al., 2018;Hsu et al., 2015). However, large-scale investigations in this area are needed to corroborate the accuracy of PM tasks as an early indicator of MCI and incipient AD in at-risk populations (i.e. SCD). In addition to utilising behavioural markers of AD in diagnosis, there is also great value in using structural biomarkers such as neuroimaging. In the following section, I will evaluate the evidence from neuroimaging studies regarding the brain regions involved in PM.

1.4 Brain regions involved in PM

Understanding the neural correlates of PM and identifying the brain regions involved in its components could potentially help target future treatments. The importance of the functional integrity of prefrontal areas in successful PM performance has been previously reported (Shallice and Burgess, 1991). Furthermore, studies demonstrated that processes utilised in PM involve structures from a wide range of neural networks such as the rostral prefrontal cortex (rPFC), the hippocampal complex and the parietal cortex (Okuda et al., 1998;Burgess et al., 2001;Burgess et al., 2003).

Neuroimaging methods (e.g. Positron Emission Tomography and functional Magnetic Resonance Imaging), show that the anterior prefrontal region, which forms a part of the Brodmann Area 10, is activated consistently with event-based PM tasks (Burgess et al., 2001;Reynolds et al., 2009). Successful PM performance also corresponds with activation in both the medial temporal lobe (Palmer and McDonald, 2000;Burgess et al., 2002) and the parietal lobe (Reynolds et al., 2009;Burgess et al., 2001;Martin et al., 2007). Considering the complex cognitive demands of PM, such as strategical detection in cue identification (prospective component) or the retrieval of an intended action (retrospective memory) (Schmitter-Edgecombe et al., 2009), it is no surprise that a range of brain areas are involved in its execution.

Temporal pole (TP) has been shown to be involved in a range of cognitive functions including, visual discrimination (Vandenberghe et al., 1995), mnemonic matching and learning (Roland et al., 1990) and semantic and episodic memory (Nakamura et al., 2001;Snowden et al., 2004). Considering the involvement of TP in cognition and processes similar to event-based PM (e.g. mnemonic matching/learning, episodic memory) and its proximity to regions involved in PM (e.g. hippocampal complex), it is likely to be a brain region involved in successful PM performance. Thus, a further aim of this study was to explore brain regions involved (i.e. rPFC and TP) in PM through the use of structural MRI.

MRI data was collected in pursuit of exploring the neural correlates of PM. Based on previous research showing that specific brain regions are involved in PM performance, MRI data was collected in this study to further explore changes in PM performance in relation to changes in brain structure. To do this, cortical thickness measures were used as a proxy of brain structure, since reduction in cortical thickness has been shown to be a biomarker linked with progression to neurodegenerative diseases such as AD (Hartikainen et al., 2012). Cortical thickness was used instead of other structural metrics (e.g. surface area or volume) due to evidence showing cortical thickness values obtained from FreeSurfer to be the most sensitive to the potential changes found between AD dementia patients and controls (Clarkson et al., 2011) as well as its strong reproducibility (Han et al., 2006;Wonderlick et al., 2009;Govindarajan et al., 2014). The reason behind using cortical thickness as opposed to grey matter volume is discussed in further detail in the following section.

1.5 Cortical Thickness vs Grey Matter Volume

In structural neuroimaging studies, there are different parameters available to use when addressing hypotheses. A variety of representations of the brain neuroanatomy can be derived using a range of automated tools such as FreeSurfer (Fischl et al., 2004) and SPM (Dahnke et al., 2013). Two of the most commonly reported results from neuroimaging studies are cortical thickness and grey matter volume. Cortical thickness is independently measured as the distance between the pial surface and white matter surface at different regions of the cortex (Fischl and

Dale, 2000), whereas grey matter volume is a function of surface area and cortical thickness (Panizzon et al., 2009). The average thickness of subcortical regions can be obtained from the FreeSurfer v6.0 pipeline (Fischl and Dale, 2000).

Where possible, analysing cortical thickness measures is recommended over grey matter volumes. One of the reasons for this is that the borders of regions of interest (ROI) are defined variably by different atlases and such variations alter regional volumes drastically. However, cortical thickness is not as affected by these variations. Hence, measuring cortical thickness is more robust to changes in definitions of boundaries, allowing us to draw conclusions that are more comparable to studies using different atlases.

The cortical thickness values obtained from FreeSurfer has been demonstrated to be robust and reproducible in previous studies (Han et al., 2006;Wonderlick et al., 2009;Govindarajan et al., 2014). Therefore, in this study, Freesurfer was used as the chosen software to obtain cortical thickness values following cortical parcellation in this study.

1.6 Aims

This study has sought to achieve the following 3 aims:

1. Investigate differences in PM performance between MCI, SCD and HC groups.

2. Explore the neural underpinnings of PM performance using structural neuroimaging.

3. Investigate the relationship between PM performance and daily functioning.

1.7 Hypotheses

1. Event-based PM scores will be lower in patients with MCI and individuals with SCD compared to HC and may herald functional decline in people destined to develop dementia.

2. The thickness of the rPFC and TP are expected to be positively correlated with PM performance.

3. PM performance reflects day-to-day functional ability as manifest through scores in Nottingham Extended Activity of Daily Living questionnaire.

1.8 Author's contribution to this study

This study was performed as a part of a larger-scale study of a PhD student (Alfie Wearn). Due to the September start date of my MSc (by research) degree, I was not able to take part in the design of the study since the project had already started in May 2017. From September 2017, I undertook the majority of recruitment and data collection. In terms of data analysis, I undertook the analysis of neuropsychological data mostly independently and with some guidance from my supervisor Liz Coulthard. The neuroimaging data analysis was undertaken in collaboration with the PhD student, Alfie Wearn, since the output from the analysis of this data formed a part of both studies. During data analysis, I also used scripts written by a former research team member, Dr Michael Knight, for data manipulation procedures. Due to the metrics specifically needed for my study, I played a major role in FreeSurfer cortical parcellation analysis, which yielded the data presented in this thesis.

2. Methods

2.1 Participants

2.1.1 Recruitment

Participants were recruited from a variety of registered databases of patients and healthy elderly people who are willing to take part in research. The majority of HCs were recruited from the Join Dementia Research database given they met the inclusion criteria. Participants with SCD were recruited from various sources including local GPs, Join Dementia Research and the Memory Clinic at the North Bristol NHS Trust. Patients with a diagnosis of MCI were also recruited from the Memory Clinic at the North Bristol NHS Trust, local GPs as well as the Avon and Wiltshire Mental Health Partnership NHS Trust's Everyone Included database.

Inclusion criteria: People with a diagnosis of MCI, age-matched individuals with SCD (defined as a self-perception of memory problems but normal performance on clinically used memory tests (e.g. ACE-III)) and age-matched HCs.

Exclusion criteria: Any significant neurological disorder that might affect test performance, History of neurosurgery, diagnosis of AD dementia or any other form of dementia.

This study is reviewed and approved by the NHS Frenchay Research Ethics Committee. Participants provided written consent to take part in this study prior to any form of testing.

2.1.2 Participant Classification

Participants were classified into the following 3 groups; HC, SCD and MCI depending on the criteria shown in **Figure 1.** Participants were nominated to be placed in the SCD group if they responded 'Yes' to 2 or more of the questions shown in **Table 1.** Subsequently, if they scored 88 or higher in the Addenbrooke's Cognitive Examination - III (ACE-III) (Crawford et al., 2012), had a Clinical Dementia Rating (CDR) score of 0 (Morris, 1993) and scored 121 or higher in the Rivermead

Behavioural Memory Test - 3 (RBMT-3), they were placed in the SCD group. Patients with a diagnosis of MCI were placed in the aMCI group. Additionally, patients with a self-report of SCD were placed in the MCI group, if they had an ACE-III score below 88 and/or an RBMT-3 score below. Lastly, if participants had an ACE-III score of 88 and above, a CDR score of 0.5 or under and an RBMT-3 score of 97.5 or higher, they were placed in the HC group.

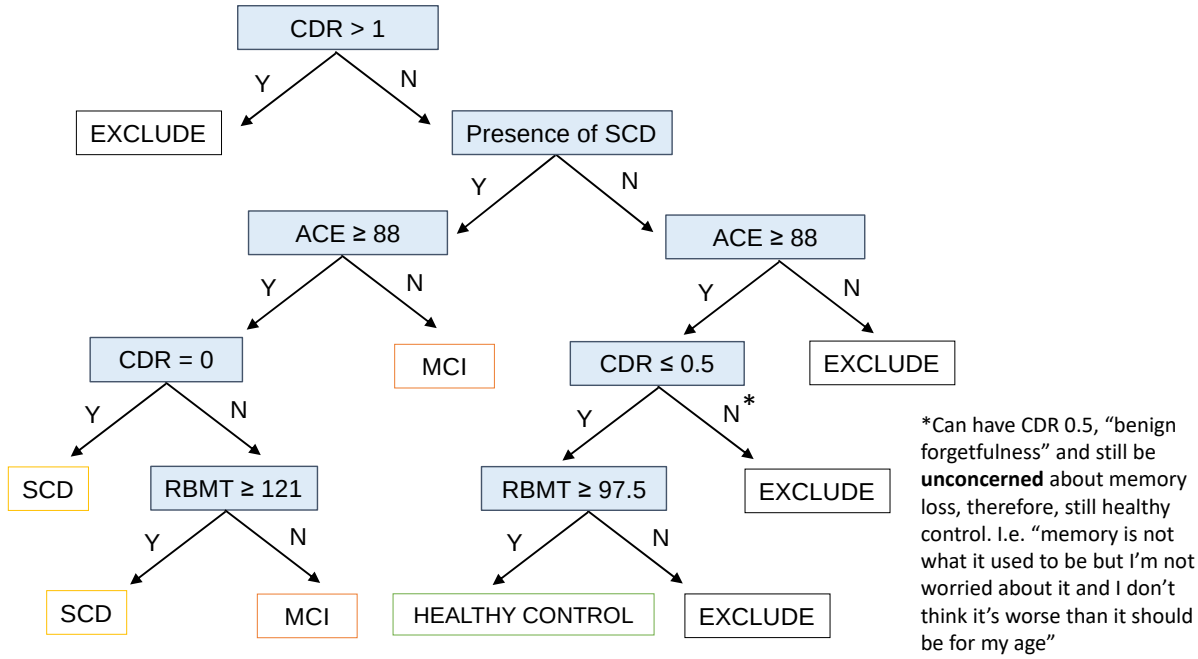


Figure 1: Classification criteria used to determine participant groups.

The RBMT-3 classification criteria was calculated as Mean scaled score -1 Standard Deviation (SD) for the SCD group and -2 SD for the HC group (Wilson et al., 2008).

Questions	**Yes / No**
Are you concerned about your memory?	Y/N
Do you think that your memory is worse than 5 years ago?	Y/N
Do you think that your memory is poorer than that of other people of a similar age?	Y/N

Table 1: Classification criteria used to determine whether participants will be placed in the SCD group.

2.2 Materials

2.2.1 Cognitive and Neuropsychological tests

Clinical Dementia Rating Scale (CDR) is a tool to measure global dementia severity using collective information regarding Memory, Home & Hobbies, Personal Care, Community Affairs and Orientation obtained from the participant and the informant. A 5-point scale is used to evaluate the participants functioning in each category. The 5-point scale is as follows: Normal (0), Questionable/Very mild dementia (0.5), Mild Dementia (1), Moderate Dementia (2) and Severe Dementia (3).
The CDR scoring algorithm was used to obtain the overall CDR score of each participant (Morris, 1993).

Rivermead Behavioural Memory Tests – Third Edition (RBMT-3) (Wilson et al., 1989) is a battery of ecological memory tests that provides information about a subject's memory performance in their daily life.

The RBMT-3 consists of the following subtests:

1. *First and Second Names:* remembering the first and second names of two people. Scoring was performed as follows:
   Each first name remembered spontaneously: 2, after a prompt: 1. Each second name remembered spontaneously: 2, after a prompt: 1. Maximum raw scores: 4 for first names and 4 for second names.

2. *Picture Recognition:* recognising 15 pictures that were previously presented and distinguishing them from a range of distractor pictures. Scoring was performed as follows:
   A score of 1 is given for each correctly recognised picture and a score of 1 is deducted from each incorrect recognition (false positives). Max raw score: 15.

3. *Appointments*: remembering to ask two questions after the alarm rings. Scoring was performed as follows:

Each spontaneously asked question: 2, after a prompt: 1. Remembering two things had to be done but not remembering what they were: 2. Remembering one thing had to be done but not remembering what it was: 1. Maximum raw score: 4.

4. *Story (immediate and delayed recall):* immediate and delayed recall of a short story. Scoring was performed as follows:
Each perfect or close synonym recall of an idea: 1, partial or approximate synonym used for each idea: ½. If the participant required a prompt a score of 1 is deducted. If a prompt is used, the first two ideas are not credited.
Maximum raw scores: immediate recall 21, delayed recall 21.

5. *Route (immediate and delayed recall):* immediate and delayed retracing of a 6-point route shown by the examiner. Scoring was performed as follows:
Each correct location visited: 1. A score of 1 was given to each of the correct starting point and finishing point. Finally, each point was considered with the next location following it. The correct recall of a pair of points was given a score of 1. Maximum raw scores: immediate recall 13, delayed recall 13.

6. *Messages (immediate and delayed recall):* immediate and delayed remembering to pick up a message and a book and deliver them to the correct location during the recall of the *Route.* Scoring was performed as follows:
Spontaneously picking up the 'Message': 2, after a prompt: 1. Spontaneously picking up the book: 2, after a prompt: 1. Leaving the message at the correct location: 1. Leaving the book at the correct location: 1. Maximum raw scores: immediate 6, delayed: 6.

7. *Face Recognition:* recognising 15 faces that were previously presented and distinguishing them from a range of distractor images. Scoring was performed as follows:
Each correctly recognised face: 1. A score of 1 was deducted for each incorrectly recognised face (false positive). Maximum raw score: 15.

8. *Novel Task (immediate and delayed recall):* remembering how to form a shape (either a star or a square) using the coloured pieces provided as well as remembering the order in which each piece is placed in the template. In the immediate recall stage, the task is repeated 3 times. In each trial the examiner demonstrates how to place the pieces to form the shape (star or square), using a specific order. In the recall stage, the participant is asked to form the shape once more with no demonstration from the examiner. Scoring was performed as follows:
For each trial; a score of 1 was given to each correctly positioned piece, a score of 1 was given to each correct order. Then, each piece was considered in turn with the piece following it and a score of 1 was given to each correctly recalled pair order. Maximum raw score for each trial: 17. Maximum raw score for immediate recall: 51. Maximum raw score for delayed recall: 17.

9. *Date and Orientation:* answering 13 questions regarding the date and orientation to time, place and person. Scoring was performed as follows:
Questions 1-3, 6-9 – A score of 1 was given to each correct answer.
Question 4 – A score of 1 was given if the answer was within half an hour of the correct time.
Questions 10-13 – A score of 1 was given if the correct first name and second name was given. A score of ½ was given for the correct surname only.
Maximum raw score: 14.

10. *Belongings:* remembering where two of their belongings are hidden. Scoring was performed as follows:
Each item recalled spontaneously: 2, after a prompt:1. Each location recalled spontaneously: 2, after a prompt: 1. Maximum raw score: 8.

Furthermore, the RBMT-3 battery offers 2 different versions that can be used in intervention studies and the assessment of follow-ups (Wills et al., 2000). Both versions were equally implemented in this study, in a randomised manner.
Activities of Daily Living Questionnaire (ADLQ) is an assessment of everyday functionality based on information provided by an informant (someone who knows the subject's daily activities and functioning) (Johnson et al., 2004). The ADLQ scale

consists of six sections covering various areas of functioning (Self-care, Household, Employment, Shopping, Travel, Communication). Each section is composed of three to six items and scored on a 4-point scale. A score of 0 (no problem) to 3 (can no longer undertake this activity) is given to each item. If the respondent chooses 9 (never done this activity/stopped before onset of dementia-related problems/don't know) as the answer, that question is not included when calculating the score for that specific subsection. The answers were scored as follows:

The formula illustrated below was used to calculate the total score, ranging from 0 to 100 **(Figure 2).** The score representing the highest level of impairment is used as the denominator (i.e. if all items were rated a score of 3), excluding the items marked "9". The total of ratings chosen by the respondent is represented by the numerator, excluding the items marked "9". Resultantly, the score obtained from the formula denotes the severity of impairment in daily functioning. Subsequently, the level of functional impairment is ranked as follows:

"None to mild" for a score of 0-33%, "Moderate" for a score of 34-66%, "Severe" for a score greater than 66%. The score of functional impairment is calculated for the total of all items as well as for each individual subscale.

$$Functional\ Impairment = \frac{Sum\ of\ all\ ratings}{3\ \times\ total\ number\ of\ items\ rated} \times 100$$

Figure 2: The formula used to calculate the functional impairment score (%) obtained from the ADLQ (Johnson et al., 2004).

Addenbrooke's Cognitive Examination (ACE-III) is one of the most commonly used clinical screening tools for the assessment of cognition in the UK (Newman et al., 2018). The ACE-III is used to detect and distinguish between different types of dementia (e.g. Alzheimer's Disease and Frontotemporal Dementia) (Hsieh et al., 2013). The 24 items in the test contribute to the assessment of five subdomains of cognition: memory (26 points), attention (18 points), language (26 points), visuospatial functioning (16 points) and fluency (14 points). The scores from all five subdomains make up the final ACE-III score out of a total of 100.

Brief Cognitive Rating Scale (BCRS) is utilised in the assessment of cognitive abilities and functionality in healthy aging as well as progressive dementia (Reisberg and Ferris, 1988). Five domains of cognition and functional abilities (Concentration, Recent Memory, Past Memory, Orientation and Functioning and Self Care) were assessed using BCRS. Each domain is rated on a 7-point scale ranging from 1 (normal) to 7 (severe impairment).

Nottingham Extended Activities of Daily Living Scale (NEADL) is used to measure independence in instrumental activities of daily living (Nicholl et al., 2002). The 22-item scale is scored on the basis of the frequency of performing each activity. The overall NEADL score is a collection of scores obtained from four generic categories of daily living: Mobility (Q1-6), Kitchen (Q7-11), Domestic (Q12-16) and Leisure (Q17-22). A score of 0 was given if the participant has chosen "never" or "with help". A score of 1 was given if the participant has chosen "on my own with difficulty" or "on my own". The maximum score is 22, where a higher score represents a higher level of independence in day-to-day functioning.

Depression, Anxiety and Stress Scale 21 (DASS 21) is a set of 3 short, self-reported questionnaires that measure levels of depression, anxiety and stress (Henry and Crawford, 2005). This questionnaire assesses the frequency of experiencing 21 symptoms over the past week and is scored on a 4-point scale in the hierarchy of 0 (never), 1 (sometimes), 2 (often) and 3 (almost always). The final scores are multiplied by 2 and categorised as shown in **Table 2.**

Severity	Depression	Anxiety	Stress
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely Severe	28+	20+	34+

Table 2: Score ranges used for the categorization of participants on DASS 21 (Henry and Crawford, 2005).

California Verbal Learning Test – Second Edition (CVLT-II) is a widely used neuropsychological test episodic verbal learning and memory, which includes a 16-item word list with words belonging to four categories (e.g. animals, clothing, tools and fruits) (Woods et al., 2006). The trials range from 1 to 5 repeats in the learning phase, where participants need to be able to recall 75% (12 words) of the list. Then a second, distractor list is read to participant once and the recalled words are recorded. The following stages of the test are short-delay free recall, short-delay cued recall, long-term free recall, long-term cued recall and recognition. At each stage, the answers are scored as either correct, repetition or intrusion.

Paired Associates Learning Task (PAL) is a neuropsychological assessment of visuospatial memory and learning. PAL has been shown to be a particularly good for predicting further cognitive decline, thus it has strong predictive validity for the development of AD (Fowler et al., 2002). A touch-sensitive, flat-screen display monitor has been used to administer this task. PAL focuses on participant's ability to associate visual patterns (that are difficult to verbalise) with spatial locations on the display monitor (Barnett et al., 2005). PAL assesses the ability to remember patterns in association with their location on the display. In this task, six white boxes, that are evenly spaced on the display, start to randomly disappear one by one for 3 seconds each. At the first level, there is only one box containing a pattern. Once all boxes have disappeared and came back, the pattern appears in the centre, and the participant is asked to touch the box this pattern was present earlier. Upon

successful completion of the level, the task moves on to the next level with more patterns to remember. If the participants fail to remember where the patterns were, the task automatically repeats itself with a maximum of 6 trials. The task starts with two levels with a single pattern, then proceeds to two levels with two patterns, followed by two levels with three patterns and then to a level with six patterns, and ultimately to a level with eight patterns. The outcome measures obtained from the test consist of trials to criterion, errors to criterion and maximum level completed.

Rey-Osterrieth Complex Figure Test (ROCFT) is a neuropsychological test used to assess visuospatial ability and memory as well as executive function mediated by the prefrontal lobe (Shin et al., 2006). This task begins with a copy condition where the participant makes a copy of the figure by looking at it. Following this, the participant is asked to draw a copy of the figure from memory in the absence of the original figure, known as the Immediate Recall condition. These 2 steps are repeated for up to a maximum of 5 times until the participant can recall 75% of the figure. Then, there is a Delayed Recall stage (20-30 minutes later), where the participant is asked to draw a copy of the figure from memory on a blank response sheet. Lastly, there is a Recognition stage, where the participant is asked to select the shapes that have made a part of the complex figure from a collection of correct and incorrect shapes. The Quantitative Scoring System (detailed in (Shin et al., 2006)) was utilised in scoring the performance on the ROCFT. The scoring of ROCFT was performed as follows:

> A score of 2 was given for each accurately drawn and correctly placed piece of the figure. A score of 1 was given if the piece was accurately drawn but incorrectly placed. Alternatively, a score of 1 was given if the piece was correctly placed but inaccurately drawn. A score of 0.5 was given to pieced that was inaccurately drawn and incorrectly placed, yet, were recognizable. A score of 0 was given to each piece that was inaccurately drawn and unrecognizable as well as being incorrectly placed, or completely omitted.

Prospective Memory test administration

In this study, the PM sub-tests from the RBMT-3 battery have been used to assess the participant's PM. The following 3 tests, which have been described above, were used:

1. *Belongings*
2. *Appointments*
3. *Messages*

Participants' performance on the 3 subtests have been assessed in 2 components of PM: "cue-identification" (prospective component) and "intention retrieval" (retrospective component). The scoring of each subtest was performed as follows:

1. *Belongings:* A score of 1 was given for the "cue-identification" component if an item or location was spontaneously remembered. Maximum raw score for "cue-identification": 4. A score of 1 was given for the "intention retrieval" component for remember each item or location either spontaneously or after a prompt. Maximum raw score for "intention retrieval": 4.

2. *Appointments:* A score of 1 was given for the "cue-identification" component if a question was spontaneously asked or for remembering something had to be done. Maximum raw score: 2. A score of 1 was given for the "intention retrieval" component for remembering each question accurately. Maximum raw score: 2.

3. *Messages (immediate and delayed recall):* A score of 1 was given for the "cue-identification" component if the message or the book was spontaneously picked up. Maximum raw score: 2. A score of 1 was given for picking up each of the correct items and placing each of them in the correct location. Maximum raw score: 4.

The total PM raw score was calculated as the sum of the raw scores from each subtest. The total PM score was then converted into a percentage by dividing the total PM raw score by the total maximum PM raw score (24) and then multiplying the result by 100.

2.2.2 Magnetic Resonance Imaging procedures

Image Acquisition

All magnetic resonance imaging (MRI) was undertaken using a Siemens Magnetom Skyra 3T system. The system was also equipped with a 32-channel head receiver array coil and a parallel transmit body coil. The imaging protocol used for the results presented in this thesis was adapted from (Knight et al., 2016) and was as follows:

3D T1-weighted Magnetisation-Prepared Rapid Gradient Echo (MPRAGE) with the parameters: sagittal, TR 2200 ms, TE 2.28 ms, TI 900 ms, flip angle 9°, FOV 220 x 220 x 179 mm, acquired resolution 0.86x0.86x0.86 mm^3, acquired matrix size 256 x 256 x 208, acquisition time 5 minutes and 7 seconds.

The rest of the protocol included 2D high-resolution hippocampal turbo spin-echo (one multi-contrast, one single contrast) with the parameters (acquisition times 5 minutes and 9 seconds and 3 minutes and 17 seconds, respectively), 2D multi-contrast spin-echo (acquisition time 7 minutes and 9 seconds) and 2D Diffusion Tensor Imaging (acquisition time 3 minutes and 15 seconds).

Image Processing and Cortical Thickness Estimation

Cortical parcellation was performed according to the Destrieux atlas of FreeSurfer version 6.0 (Fischl et al., 2004). 3D T1-weighted MPRAGE images were used in the surface-based cortical parcellation process (**Figure 3**). The methods for cortical parcellation using FreeSurfer have been described in detail in other studies (Dale et al., 1999;Fischl and Dale, 2000;Rosas et al., 2002;Salat et al., 2004;Fischl et al., 2004).

In brief, the automated cortical parcellation procedure includes processes such as normalisation of intensity, skull stripping, cerebral white matter segmentation as well as the estimation of the grey/white matter boundary (Dale et al., 1999). Following topological defect corrections, the grey/white matter boundary is used to locate the pial surface and cortical thickness was then measured (Fischl and Dale, 2000). This method has been validated (Rosas et al., 2002) and it has been shown to be reliable (Han et al., 2006;Dickerson et al., 2008).

The following regions were used in data analysis:
G&S_transv_frontopol region was used to determine rPFC cortical thickness values.
Pole_temporal region was used to determine the TP cortical thickness values.
Pole_occipital region was used to determine Occipital Pole (OP) cortical thickness values, to be used as a control region.

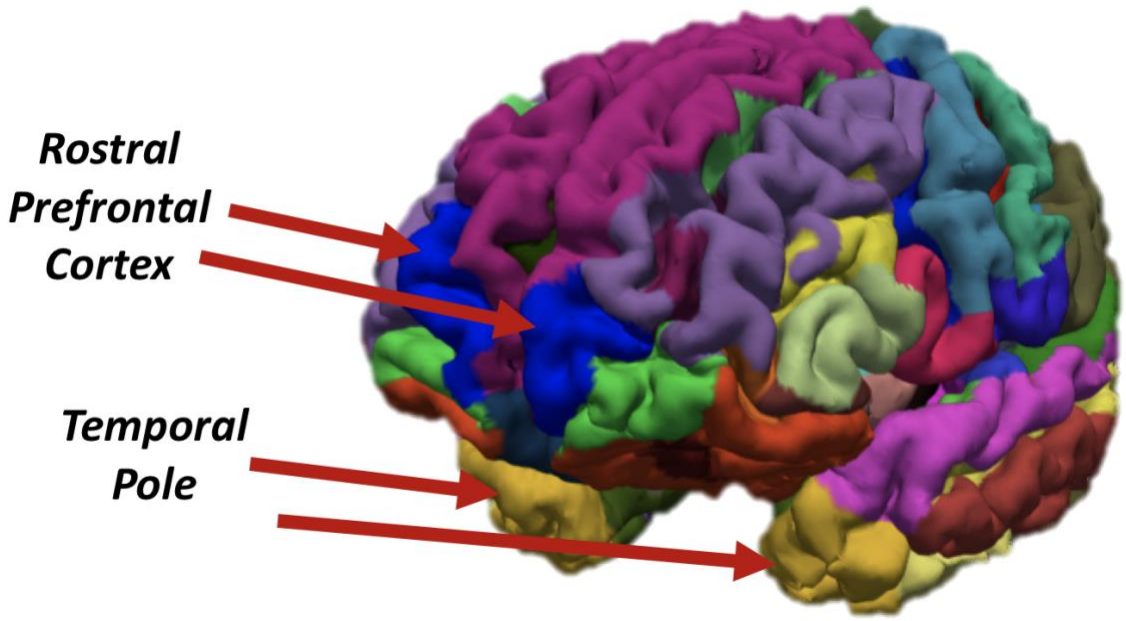


Figure 3: Pial surface representation of the automated cortical parcellation procedure carried out using FreeSurfer version 6.0 (Fischl et al., 2004). Colours represent different cortical regions in the Destrieux atlas.

2.2.3 Statistical Analyses

All statistical analyses were performed using IBM SPSS version 24. GraphPad Prism version 7, IBM SPSS version 24 and Microsoft Office software (Excel and PowerPoint) were used for visualisation of results in various forms (e.g. graphs, tables). All demographic data was explored, and normality was checked through the Descriptive Statistics function of SPSS. A Pearson's chi-squared test was run to check for gender balance within groups. A univariate analysis of variance (ANOVA) was performed to check whether there was an age difference between groups. Since the data violated assumptions of normality and age was identified as a covariate, the non-parametric analysis of covariance test, Quade's test, was performed with post hoc pairwise comparisons to compare PM performance across groups. Since the data did not meet the assumptions of normality and age was a covariate, the partial correlation test was run to investigate the relationship between PM performance and NEADL. The same correlation analysis was run on PM performance and average thickness of rPFC and TP. In these correlation analyses the whole participant population was combined and compared against the dependent variable (i.e. ROI cortical thickness or NEADL scores). Group-based correlations were not carried out, due to the lack of statistical power of individual groups as a result of small sample sizes.

In all analyses, $p < 0.05$ was accepted as statistically significant. In instances where multiple comparisons were undertaken, a Bonferroni correction for multiple tests was used. Left and right hemispheres were averaged to calculate average cortical thickness in each brain region. This was done to account for differences in hemispheres between individuals, since there were both right and left-handed individuals in the study.

3. Results

3.1 Demographic characteristics of the participant sample

The demographics of the sample together with the average performance on the tests used in this study are presented in **Table 3**.

	HC	SCD	MCI	P value
Age (years) **Age range**	71.40 ±7.51 61 - 89	71.10 ±8.14 55 - 86	78.59 ±9.16 53 - 94	0.068
Gender (male)	46.15%	58.62%	68.96%	0.230
Years of Education (years)	15.92 ±4.08	15.58 ±3.55	13.71 ±3.16	0.054
IQ	108.91 ±11.08	107.68 ±9.14	104.00 ±9.14	0.101
Performance on Neuropsychological Tests used in classification				
ACE-III	95.55 ±2.37	93.85 ±3.73	79.47±8.37	0.856
RBMT-3	162.25 ±16.87	149.43 ±21.51	91.77 ±26.47	0.988

Table 3: Summary of the demographic data of all 3 participant groups. (RBMT-3 scores represent raw scores) (Results across groups represent Mean ±SD, except ranges and percentages)

3.2 The effect of Age

The effect of age on PM performance:
A spearman's rank-order correlation test revealed that age is neatively correlated with PM performance ($N = 84$, $r_s = 0.451$, $p < 0.001$). Subsequent to this finding, a parametric one-way ANOVA was run to check whether the distribution of age was the same across groups. The results of this analysis demonstrated that there was no difference in age between groups ($p = 0.068$).

The effect of age on ROI thickness:
A spearman's rank-order correlation test showed age was not significantly correlated with either average rPFC or TP thickness ($N = 62$, $r_s = 0.156$, $p = 0.225$ and $r_s = 0.092$, $p = 0.480$, respectively).

Since age was only correlated with PM scores, it was controlled as a covariate in all analyses including PM scores.

3.3 PM Performance across Groups

Event-based PM performance was compared across 3 groups; HC (N = 26), SCD (N = 29) and MCI (N = 29).

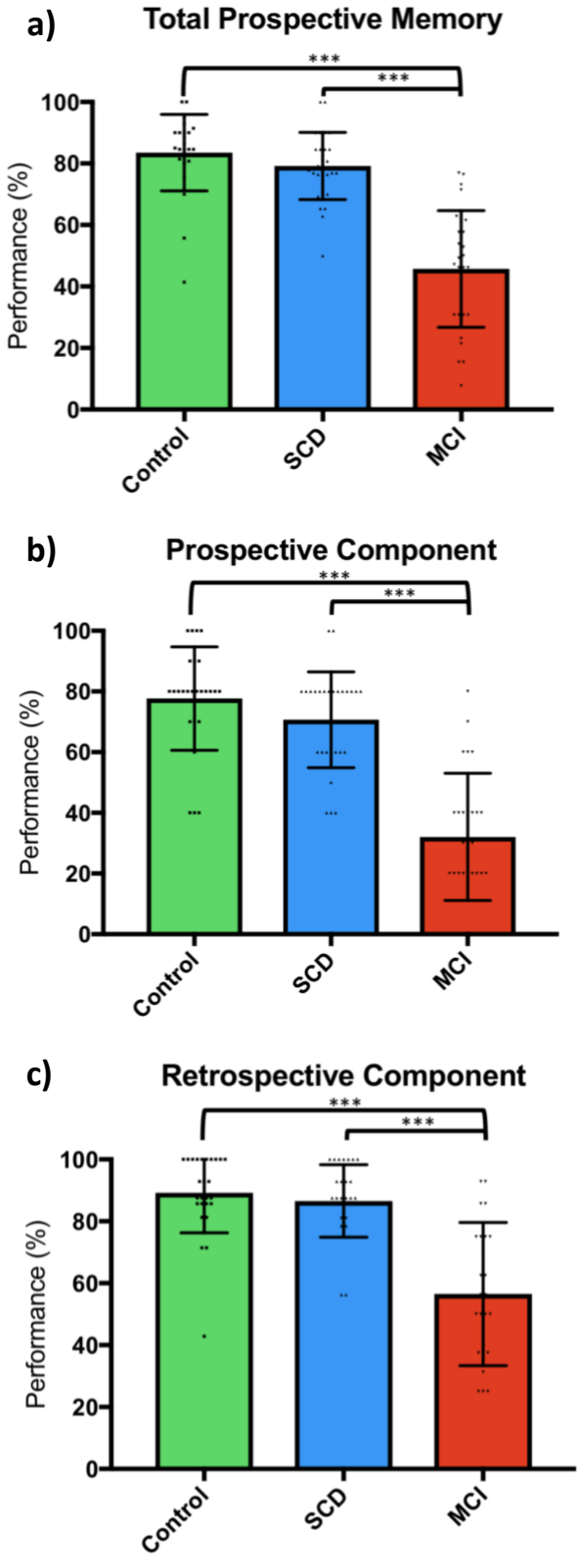


Figure 4: The performance of the 3 groups in prospective memory tasks presented as total PM score (%) as well as prospective component and retrospective component (*** = $p < 0.001$) (N = 84).

(Error bars represent SD)

Total Prospective Memory: A significant difference of means across groups was found (Quade's F (2,81) = 39.14, $p < 0.001$) (shown in **A** of **Figure 4**). Following this, post hoc tests with Bonferroni corrections were conducted to test pairwise comparisons. The MCI group (M = 48.34, SD = 19.89) was significantly different from HC (M = 86.45, SD = 7.32) ($p < 0.001$) and SCD (M = 80.66, SD = 9.70) ($p < 0.001$). However, there was no significant difference between the HC and SCD groups ($p = 0.078$).

Prospective Component: A significant difference of means across groups was found (Quade's F (2,81) = 33.98, $p < 0.001$) (shown in **B** of **Figure 4**). Following this, post hoc tests with Bonferroni corrections were conducted to test pairwise comparisons. The group (M = 34.12, SD = 18.39) was significantly different from HC (M = 81.00, SD = 14.47) ($p < 0.001$) and SCD (M = 73.00, SD = 13.80) ($p < 0.001$). However, there was no significant difference between the HC and SCD groups ($p = 0.180$).

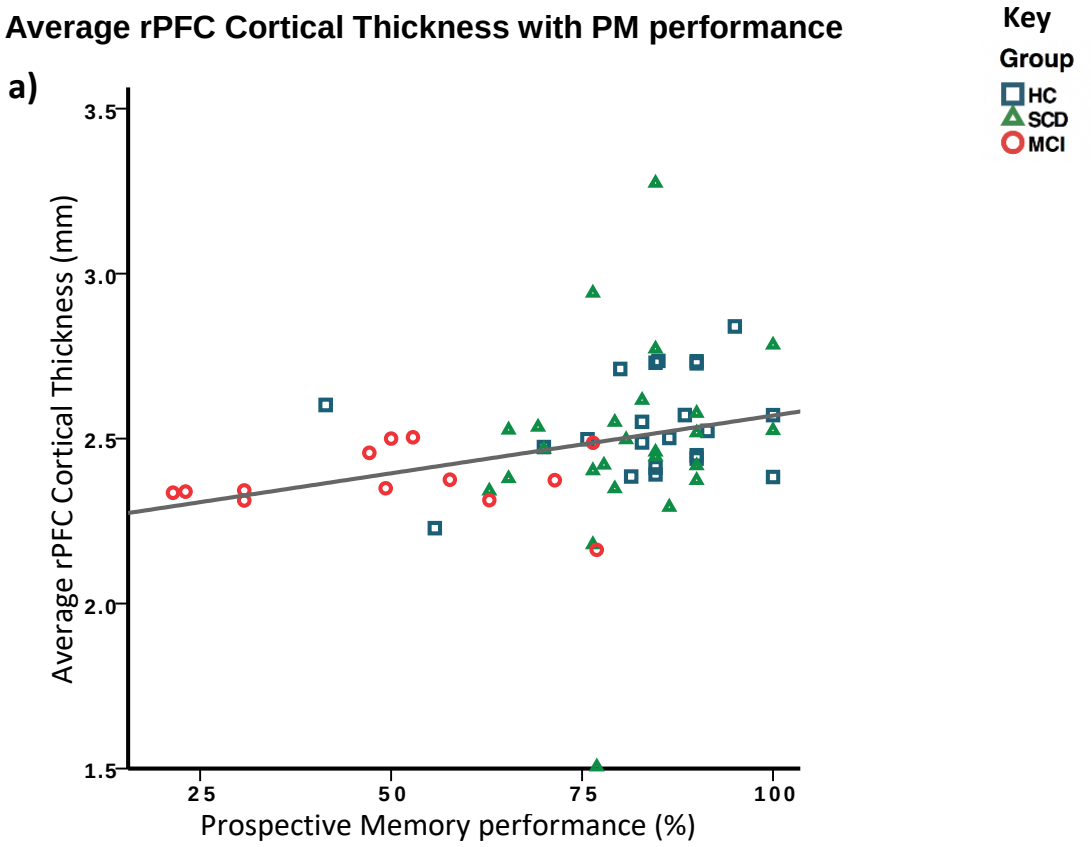
Retrospective Component: A significant difference of means across groups was found (Quade's F (2,81) = 21.40, $p < 0.001$) (shown in **C** of **Figure 4**). Following this, post hoc tests with Bonferroni corrections were conducted to test pairwise comparisons. The MCI group (M = 61.13, SD = 26.45) was significantly different from HC (M = 91.96, SD = 8.62) ($p < 0.001$) and SCD (M = 87.86, SD = 11.03) ($p < 0.001$). However, there was no significant difference between the HC and SCD groups ($p = 0.777$).

3.3 The relationship between PM and Cortical Thickness

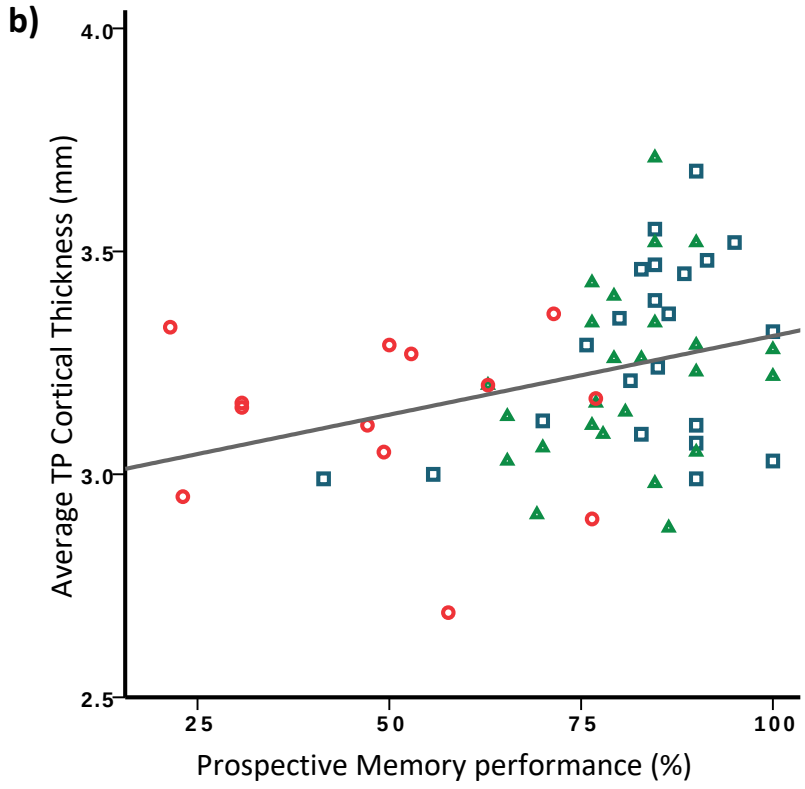
	HC	SCD	MCI	Quade's Test p-value	Post-hoc p-value (if applicable)
Average rPFC thickness	2.53 ±0.15	2.49 ±0.30	2.37 ±0.01	0.009	HC-MCI = 0.007 SCD-MCI = 0.090 HC-SCD = 0.664
Average TP thickness	3.27 ±0.20	3.22 ±0.20	3.13 ±0.19	0.246	N/a
Average OP thickness	2.11 ±0.15	2.04 ±0.10	2.04 ±0.19	0.163	N/a
Average Whole Brain thickness	2.49 ±0.11	2.44 ±0.07	2.35 ±0.09	0.009	HC-MCI = 0.008 SCD-MCI = 0.413 HC-SCD = 0.149

Table 4: The cortical thickness values (mm) of 3 brain regions (2 ROIs and 1 Control) and the whole brain. (Results across groups represent Mean ±SD).

Average rPFC Cortical Thickness with PM performance



Average TP Cortical Thickness with PM performance



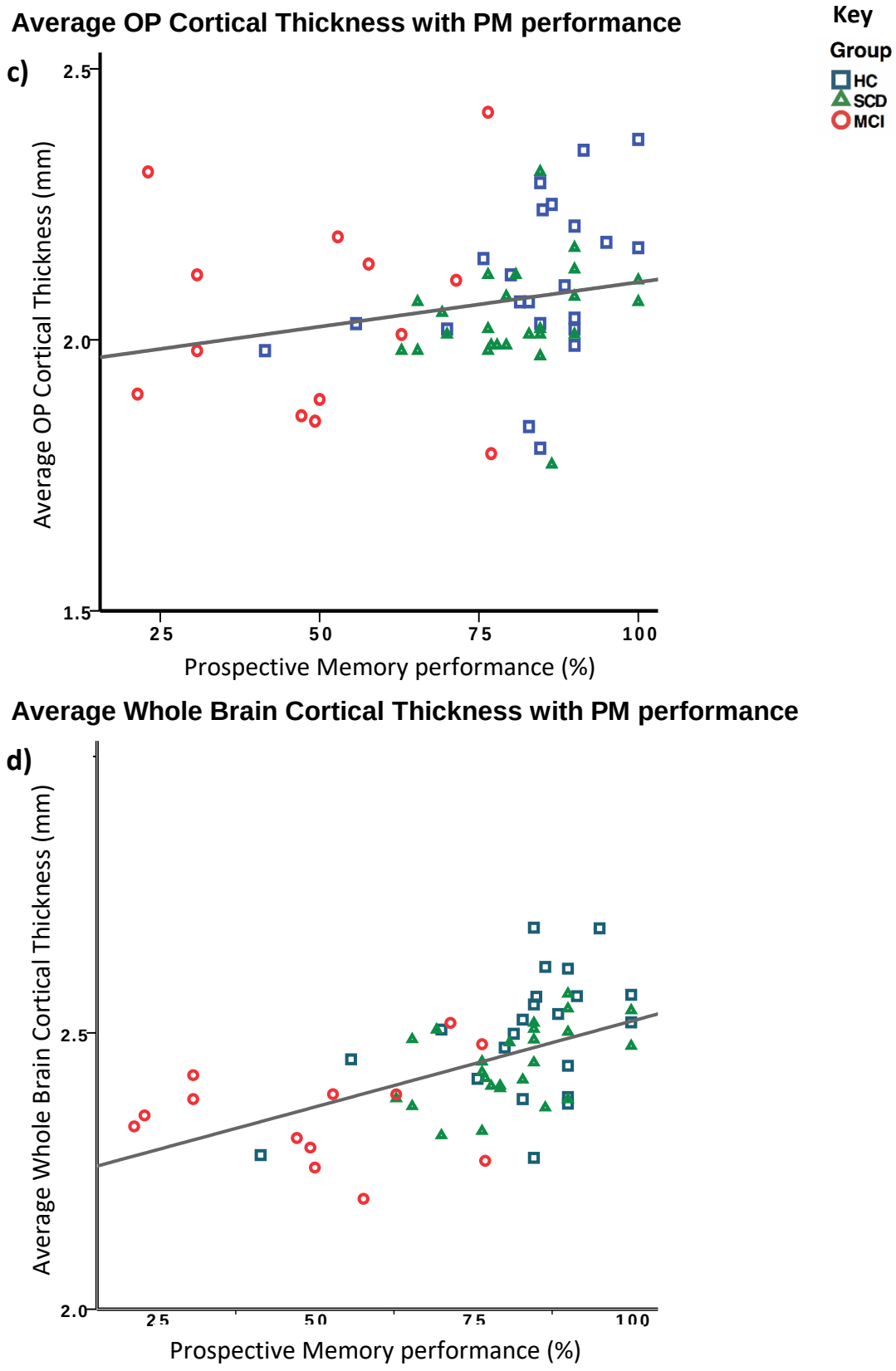


Figure 5: The scatter plots illustrate the relationship between PM performance and the thickness of **a)** Rostral Prefrontal Cortex (rPFC), **b)** Temporal Pole (TP), **c)** Occipital Pole (OP) and **d)** Whole Brain.

The average thickness of each brain region across groups as well as the whole brain is illustrated in **Table 4** in the form of Mean ± SD.

A partial correlation was performed to investigate the relationship between PM performance and **a) rPFC** and **b) TP**, whilst controlling for age, as illustrated in **Figure 5**. The results showed that PM performance and the average thickness of rPFC were positively correlated with high statistical significance ($N = 62$, $r = 0.439$, $p < 0.001$). Furthermore, there was also a strong positive correlation, which was statistically significant, between PM performance and the average thickness of TP ($N = 62$, $r = 0.344$, $p = 0.007$).

The total PM performance was found to be correlated with the thickness of the control region (**c) OP** in **Figure 5**) ($N = 62$, $r = 0.263$, $p = 0.041$). However, when investigating the relationship between OP thickness and the prospective component on PM, there was no significant correlation found ($r = 0.222$, $p = 0.086$). Yet, there was a positive correlation between prospective component of PM and both rPFC and TP thicknesses which was highly significant ($r = 0.432$, $p < 0.001$ and $r = 0.365$, $p = 0.004$, respectively). The retrospective component of PM had the higher correlation with rPFC ($r = 0.778$, $p = 0.001$) compared to OP ($r_s = 0.344$, $p = 0.007$). There was no significant correlation between the retrospective component of PM and the TP ($r = 0.202$, $p = 0.118$).

Following results shown above, a posthoc analysis of whole brain cortical thickness and PM performance has been conducted to investigate whether PM performance is correlated with cortical thickness of the whole brain. A partial correlation analysis of the relationship between average whole brain cortical thickness and PM performance, whilst controlling for age, showed a moderate and significant correlation ($r = 0.490$, $p < 0.001$).

3.5 The relationship between PM and Activities of Daily Living

A partial correlation analysis was performed to investigate the relationship between total PM score and the NEADL score. The results showed that there was a strong positive correlation between PM performance and the NEADL score with high statistical significance, whilst controlling for age ($N = 71$, $r = 0.255$, $p = 0.033$). Furthermore, the relationship between the two components of PM (i.e. prospective component and retrospective component) with NEADL was also investigated in the same manner. The outcome of this analysis showed that the prospective component was not significantly correlated with NEADL ($N = 71$, $r = 0.201$, $p = 0.095$). The retrospective component is significantly correlated with NEADL ($N = 71$, $r = 0.329$, $p = 0.005$).

4. Discussion

4.1 Differences in PM performance across Groups

The results shown in **Figure 4** demonstrate that the MCI group performance in event-based PM tasks was significantly worse than the HC and SCD groups, partially supporting **Hypothesis 1.** However, no significant difference in the performance of the HC and the SCD groups was observed in the event-based PM tasks. Hence for the second half of **Hypothesis 1,** the null hypothesis is accepted.

As demonstrated in this study, the MCI group had an impairment in evet-based PM, supporting previous findings (Kazui et al., 2005;Troyer and Murphy, 2007;Karantzoulis et al., 2009;Bolló-Gasol et al., 2014). Yet, no difference between the SCD and HC groups was observed, contrary to the hypothesis. This suggests that the SCD group may not differ from the HC group in event-based PM tasks, despite previously being reported to differ in time-based PM tasks (Hsu et al., 2015). However, it is difficult to make concrete statements regarding the difference in event-based PM between the SCD and HC groups since this has not yet been extensively studied. One of the reasons that there was no difference observed could be due to

the nature of the lab-based tests not being able to detect such subtle changes in PM performance in pre-MCI groups (i.e. SCD). A recent study by Lee et al. (2018), demonstrated that a difference between the SCD and HC groups in PM was detected when they used more naturalistic tasks of PM with stronger resemblance of real life day-to-day functioning (e.g. The Supermarket Shopping Trip Task (Kinsella et al., 2009)). Thus, further research is needed to investigate whether there is a difference in event-based PM between performance between the HC and SCD groups.

4.2 PM performance and Cortical Thickness

In accordance with the results reported above and illustrated in **Figure 5,** the null hypothesis that there is no positive correlation between the average thickness of the ROIs (i.e. rPFC and TP) and PM performance is rejected. Although **Hypothesis 2** was confirmed, there was also a significant correlation between PM performance and the control region, OP, which is thought to be unrelated to PM. Hence, in this instance, it is not possible to make direct inferences regarding a potential relationship between the cortical thinning of specific brain areas (i.e. rPFC and TP) and PM impairment. In addition, it is very difficult to make statements about a causal relationship between two parameters (e.g. Cortical Thickness and PM performance) from a cross sectional study such as this. In future experiments, a longitudinal experimental design such as studying a group of individuals over a period of 10 years whereby neuropsychological assessment and neuroimaging is undertaken at regular intervals (e.g. every 6 months) could be a better way of investigating a causal relationship. Alternatively, use of different methodology such as functional MRI would allow exploring the relationship between blood oxygen-level dependent signals from specific brain regions and PM performance. A further alternative method could be the use of transcranial magnetic stimulation on specific brain regions to study the direct relationship between the activation/stimulation of a specific brain region and its influence on function (e.g. PM performance).

Furthermore, it is important to note that the MCI population is highly heterogeneous where only a part of the patient population will develop AD pathology and the rest will

have other disorders or recover (Libon et al., 2010;Delano-Wood et al., 2009;Koepsell and Monsell, 2012). Even the part of the MCI group that will develop AD pathology might have a range of comorbidities rather than solely AD (Grande et al., 2016;Tsolaki et al., 2016). Hence, studying the effects of specific brain regions on a memory type in a heterogeneous group, such as MCI, is highly challenging. To truly explore the effects of a brain region on a memory type, the aforementioned future experiments can be implemented (e.g. use of transcranial magnetic stimulation).

One of the interesting outcomes of this study was that PM is correlated with general cortical thinning. This is supported by the finding that there was a significant correlation between PM and the OP, a brain region thought to be insignificant to PM performance. Hence, based on the evidence from this study, it is thought that PM performance is correlated with general cortical thinning as opposed to cortical thinning of specific brain regions in preclinical AD groups. As mentioned above, there could be a range of reasons why there was no significant correlation between PM performance and specific brain regions. One reason could be that the majority of the patient population had MCI that would revert to normal cognition or had MCI due to other neurological conditions than AD. Furthermore, using structural MRI might not be sensitive enough at preclinical stages of AD to study the relationship between specific brain regions and cognitive/memory subdomains/subtypes. It could be argued that functional MRI or positron emission tomography might be better tools to study direct activation of specific brain regions in preclinical AD populations during event-based PM tasks. Nevertheless, this finding supports the use of event-based PM tests in memory clinics as a guide to early functional decline in incipient AD.

The cortical thickness of rPFC had the strongest correlation with PM, as well as its prospective and retrospective components compared to the other 2 brain regions (TP and OP) investigated in this study. This finding is in line with Burgess et al. (2003), supporting the importance of rPFC in successful PM performance. Moreover, the TP was also found to be highly correlated with only the prospective component of PM, suggesting TP might play an important role in the cue-identification phase of PM.

4.3 PM performance and Activities of Daily Living

Both components of PM have been found to be correlated with functional independence in daily life (as measured by NEADL scores) in accordance with Burgess et al. (2000). Furthermore, the retrospective component was found to have a greater impact on functional independence than the prospective component. This suggests that the retrospective component could compensate for the impairment in the prospective component in day-to-day activities. Thus, when the retrospective component is also impaired, a greater impact on day-to-day functioning and the independence of patients could be expected.

Due the its high functional relevance, problems in PM have been found to be one of the most commonly reported early signs of AD (Smith et al., 2000). In addition to this, carers reported that PM failures were even more burdensome than retrospective memory impairment, supporting the importance of PM in everyday functioning (Smith et al., 2000). Hence, providing further evidence for the value of PM tasks as a guide to early functional decline in preclinical AD.

4.4 Methodology for cortical thickness measurement and event-based PM

FreeSurfer was chosen to perform the automated cortical parcellation in this study. This software was selected because of its high reliability for cortical thickness measurement (Han et al., 2006). 3D T1-weighted MPRAGE images were used in the cortical parcellation process to obtain average cortical thickness of ROIs, which has been shown to be accurate, especially compared to other scan types (e.g. 2D spin-echo images) (Vidal-Jordana et al., 2017).

RBMT-3 was the selected cognitive test battery due to its high ecological validity and the variety of tests included to assess multiple domains of cognition. RBMT has been found to correlate with conventional tests of episodic memory (e.g. the Weschler Memory Scale and CAMCOG), commonly used for diagnostic purposes (Makatura et al., 1999;Perez and Godoy, 1998;Yassuda et al., 2010). Additionally, RBMT-3 is able to differentiate between HC, MCI and AD groups (Yassuda et al., 2010;Kazui et al.,

2005). As the event-based PM tasks were a subset of RBMT-3, our results are strengthened by the good reliability of the test battery (Küçükdeveci et al., 2009).

However, the total RBMT-3 scaled score was used as a final stage classifier to categorise individuals into groups, following CDR and ACE-III scores. Therefore, one could argue that the between group differences found in PM performance could be due to the event-based PM tasks being a subtest of RBMT-3, originally used as a factor in participant classification. Yet, the 3 event-based PM subtests make up a very small part of the total RBMT-3 score and in most cases, the RBMT-3 score was not required for classification since the CDR and ACE-III were used prior to RBMT-3 for grouping participants.

5. Conclusion & Future Work

PM performance was found to be a strong indicator of day-to-day functioning in this study. Moreover, PM performance was also found to correlate with imaging biomarkers of early cognitive decline. The findings from the neuroimaging aspect of the study support the findings of other neuroimaging studies regarding the relationship between cortical thickness and PM performance (Burgess et al., 2001;Reynolds et al., 2009). Thus, our results demonstrate cross-method concordance. Overall, the outcomes of this study provide a valuable insight into the use of PM performance as a guide to functional decline in the very early stages of AD.

Participants will be contacted for a 1-year follow-up in which they will undertake another MRI scan as well as further neuropsychological assessment. One important additional aspect of the follow-ups is that participants will also undertake two time-based prospective memory tasks. This will enable us to examine whether participants' performance differ in time-based PM tasks compared to event-based ones. Furthermore, this new aspect of the study will create an opportunity to validate previous research by others (Troyer and Murphy, 2007;Karantzoulis et al., 2009;Hsu

et al., 2015), where Hsu and colleagues reported there was greater impairment in time-based PM performance than event-based PM tasks. The 1-year follow-ups will also show whether event-based PM tasks are predictive of cognitive decline.

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